

A New Hybrid Phosphine Ligand for Palladium-Catalyzed Amination of Aryl Halides

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Abstract: A new hybrid phosphine was designed. The phosphine combines two common structural characteristics found among the effective phosphine ligands reported recently, namely, three *tert*-alkyl substituents binding to the phosphorus and an aryl group at an appropriate position. A hybrid phosphine/palladium system is versatile and effective for the coupling reaction of various aryl halides with primary and secondary amines including carbazole.

Keywords: amination; cross-coupling; ligand design; P ligands; palladium

Triaryl amines are an important class of structures for pharmaceuticals, fine chemicals and new materials. One of the most powerful methods of preparing them is the palladium-catalyzed coupling reaction of aryl halides with amines.^[1,2] For a successful coupling reaction, the choice of an appropriate ligand is essential because the nature of the ligands has an important effect on the coupling. Indeed, the use of newly developed phosphine ligands, such as those shown in Figure 1, has greatly improved the efficiency of the coupling reaction.^[3–9] For example, the Koie group employed tris(*tert*-butyl)phosphine **4** as a ligand for the coupling and demonstrated its capability.^[3] The Buchwald group has reported biarylmonophosphine ligands **2**, which are effective for a wide range of aryl halides.^[4] We have also reported the coupling reaction using diphenylvinylphosphine ligands **1** that have a similar structure to ligand **2**.^[5]

The phosphine ligands in Figure 1 can be classified into two types according to their structural characteristics: (1) phosphines having aryl groups at an appropriate position fixed by their spacers (ligands **1–3**, category 1); and (2) phosphines bearing three *tert*-alkyl substituents (ligands **4** and **5**, category 2). We envi-

sioned that further improvement was feasible if we designed and synthesized a phosphine combining both characteristics. This idea encouraged us to develop the new hybrid phosphine ligand **6** (Figure 2). The ligand has two *tert*-butyl groups and a methylcyclopropane moiety binding to the phosphorus, as is characteristic of ligands in category 2; it also has virtually the same spatial relationship between the phosphorus and the phenyl group as ligand **1** in category 1.

Phosphine ligand **6** was synthesized in two steps from commercially available starting materials.^[10] Reaction of 1,1-diphenylethylene with a carbene species,

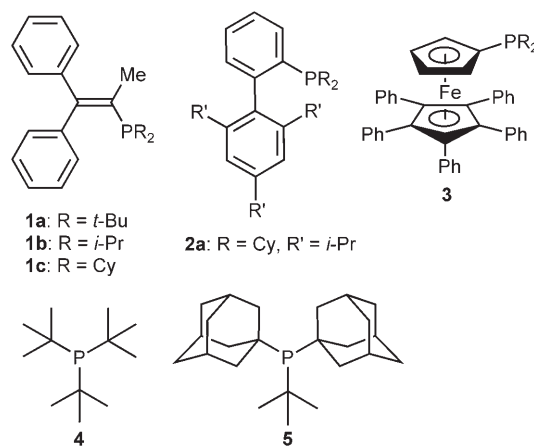


Figure 1. Structures of reported phosphine ligands.

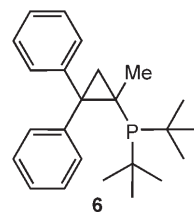
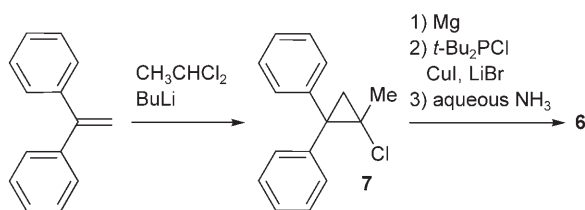


Figure 2. Structure of phosphine ligand **6**.



Scheme 1. Preparation of ligand **6**.

generated *in situ* from BuLi and 1,1-dichloroethane, gave a chlorocyclopropane in 77% yield. Subsequent phosphination by forming a Grignard reagent from the chlorocyclopropane and magnesium turnings and reacting it with di-*tert*-butylchlorophosphine in the presence of copper iodide and lithium bromide, afforded the phosphine **6** as a solid that is stable to air and moisture (Scheme 1).

To evaluate the performance of ligand **6**, we first compared it with diphenylvinylphosphine ligands **1a** and **1b** that we had previously reported.^[5] For the reaction of 4-bromoanisole with diphenylamine in the presence of 1 mol% of Pd, all three ligands were effective enough to bring the reactions to completion. However, at lower catalyst loading (0.1 mol% of Pd), ligand **6** gave 97% yield in 3 h while ligands **1a** and **1b** gave only 39% and 26%, respectively (Scheme 2). This result represents significant improvement as reduced catalyst loading is increasingly expected.

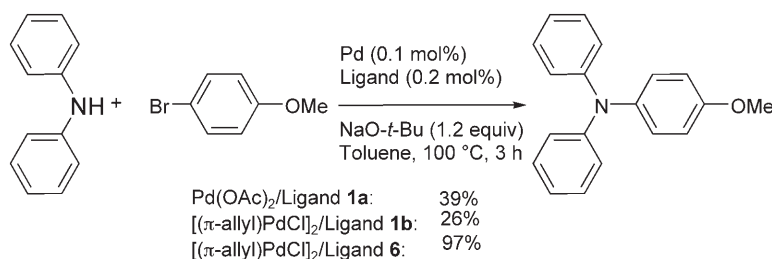
Then we examined the coupling of general aryl halides with amines using ligand **6**. As shown Table 1, ligand **6** shows its generality for various substrates.^[10] The reaction of bromomethylenedioxybenzene with diphenylamine, which was carried out in toluene at 100 °C in the presence of 2 mol% of ligand **6** and 0.5 mol% of $[(\pi\text{-allyl})\text{PdCl}]_2$, gave the coupling product in 97% yield (entry 1). Aryl chlorides bearing electron-donating groups such as 4-methoxy and 3-methyl groups were smoothly converted to the corresponding amines in excellent yields (entries 3 and 5). In the case of *ortho*-substituted aryl chloride, the isolated yield was 80% with elevated temperature (entry 2). In entries 6–8, anilines reacted with 1 and 2 equiv. of aryl halides to afford corresponding secondary and tertiary amines. Reactions of indole with bromo- and chloro-

benzene successfully proceeded as well (entries 9 and 10).

In the development of new materials such as light-emitting diodes and organic photo conductors, carbazole derivatives have attracted great attention due to their unique electric properties.^[11] For example, 4,4'-dicarbazolebiphenyl (CBP) and its analogues are well-known as a host material used in the thin light-emitting layer of such devices.^[12] For the preparation by a palladium-catalyzed coupling reaction, Hartwig's group has reported that the coupling reaction of 4-cyanophenyl bromide with carbazole using a DPPF/Pd(OAc)₂ catalyst system gave the corresponding product in 97% yield.^[13] Koie's group has shown that a system consisting of ligand **4**/Pd(OAc)₂ and K₂CO₃ was effective in the preparation of carbazole derivatives.^[14] They also applied the system to the reaction of 4-formylphenyl chloride to give the product in 71% yield.

With the ligand **6**/Pd system, we started studies on the coupling reaction of carbazole. The results are summarized in Table 2. Under the same conditions as in Table 1, the reactions of bromo- and chlorobenzenes were successfully completed in 3 h to afford *N*-phenylcarbazole in 98% and 94% isolated yields, respectively (entries 1 and 2). Ligand **6** was then applied to the reaction of aryl chlorides substituted with electron-donating and -deficient groups. In the reaction of 4-chlorobenzonitrile at 80 °C, the corresponding product was obtained in 93% yield (entry 3). When chloroarenes with electron-donating groups were used, the ligand **6**/Pd system effectively catalyzed the reactions as well (entries 4 and 5). In addition to these results described above, we tried the reaction of 1,3,5-trichlorobenzene with 3 equiv. of carbazole. The coupling was successfully carried out to give the sterically hindered coupling product, tricarbazolebenzene, in good yield after purification by recrystallization from toluene.

In summary, we developed a new hybrid phosphine ligand **6**, which combines two structural characteristics; three *tert*-alkyl substituents binding to the phosphorus, and an appropriate spatial relationship between the phosphorus and the phenyl group. The ligand **6**/palladium system performed well for the cou-



Scheme 2. Coupling of 4-bromoanisole with diphenylamine.

Table 1. Coupling of aryl halides with amines.^[a]

Entry	Amine	Aryl halide	Product	Yield ^[b] [%]
1				97
2 ^[c]				80 ^[d]
3				95
4 ^[e]				90
5				98
6 ^[f]				91
7 ^[f]				90
8 ^[g]				95
9				84
10 ^[c,h]				82

^[a] Reaction conditions: amine (1.0 equiv.), aryl halide (1.1 equiv.), [(π -allyl)PdCl]₂ (0.5 mol%), ligand **6** (2 mol%), NaO-*t*-Bu (1.2 equiv.), toluene, 100 °C, 3 h.

^[b] Isolated yield.

^[c] Reaction was conducted in xylene at 120 °C.

^[d] 90% GC conversion.

^[e] Amine (2.2 equiv.), aryl halide (1.0 equiv.) and NaO-*t*-Bu (2.4 equiv.) were used.

^[f] Aryl halide (2.2 equiv.) and NaO-*t*-Bu (2.4 equiv.) were used.

^[g] Aryl halide (1.0 equiv.) and NaO-*t*-Bu (1.1 equiv.) were used.

^[h] [(π -allyl)PdCl]₂ (1.0 mol%) and ligand **6** (4 mol%) were used.

Table 2. Coupling of aryl halides with carbazole^[a].

Entry	Aryl halide	Product	Yield ^[b] [%]
1			98
2			94
3 ^[c]			93
4			95
5			95
6 ^[d]			67 ^[e]

^[a] Reaction conditions: carbazole (1.0 equiv.), aryl halide (1.1 equiv.), [(π -allyl)PdCl]₂ (0.5 mol%), ligand **6** (2 mol%), NaO-*t*-Bu (1.2 equiv.), xylene, 120 °C, 3 h.

^[b] Isolated yield.

^[c] Reaction was conducted at 80 °C. When run at 120 °C, the yield was 64%.

^[d] Aryl chloride (1.0 equiv.), carbazole (3.3 equiv.), [(π -allyl)PdCl]₂ (1.5 mol%), ligand **6** (6 mol%) and NaO-*t*-Bu (3.6 equiv.) were used.

^[e] The HPLC conversion was > 99%.

pling reactions of various aryl chlorides. In the reaction of carbazole, ligand **6** provides a useful method of the preparation of derivatives. Further applications are under investigation.

Experimental Section

Procedure for the Preparation of **7**

Butyllithium (1513 mL, 1.54 M in hexane, 2.33 mol) was added dropwise to a solution of 1,1-dichloroethane (461 g, 4.66 mol) and 1,1-diphenylethylene (210 g, 1.17 mol) in CPME (1260 mL) at –35 to –40 °C under a nitrogen atmosphere. After the solution had been stirred for 30 min, the reaction was quenched by the addition of water (1000 mL) at 0 °C. The organic phase was then separated, washed with water (1000 mL $\times$ 2) and concentrated under reduced pres-

sure. The concentrate was purified by recrystallization from MeOH (1000 mL) to give the title compound as a white solid; yield: 218 g (77%). ^1H NMR (300 MHz, CDCl_3): δ = 1.57 (s, 3H), 1.67 (d, J = 6.7 Hz, 1H), 1.87 (d, J = 6.7 Hz, 1H), 7.12–7.32 (m, 6H), 7.42 (br d, J = 6.9 Hz, 2H), 7.50 (dt, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 27.0, 28.3, 42.5, 48.6, 126.6, 126.7, 128.1, 128.6, 129.1, 129.8, 142.2, 142.9.

Procedure for the Preparation of 6

A small amount of iodine and *t*-BuMgCl were added to a solution of magnesium turnings (18.2 g, 0.754 mmol) in THF (73 mL) at room temperature under a nitrogen atmosphere. After stirring for 3 h, a solution of compound 7 (174 g, 0.718 mol) in THF (523 mL) was added dropwise to the premixed solution. The reaction solution was stirred at 65 °C overnight and then cooled to room temperature. The resulting solution was added dropwise to a solution of CuI (145 g, 0.761 mol), LiBr (68.6 g, 0.790 mol) and di-*tert*-butylchlorophosphine (143 g, 0.790 mol) in THF (699 mL) at 55 °C. After stirring for 6 h, hexane (900 mL) was added at 35 °C and the mixed solution was cooled to 10 °C. A generated copper salt was separated by filtration and dissolved with toluene. The toluene solution was washed with aqueous ammonia under air until the color of the solution change from blue to colorless. After washing with water, the solution was concentrated under reduced pressure. The concentrate was purified from methanol (930 mL) to give the title compound as a white solid; yield: 162 g (64%). ^1H NMR (500 MHz, CDCl_3): δ = 1.22 (d, J = 13.1 Hz, 9H), 1.28–1.33 (m, 1H), 1.31 (d, J = 6.3 Hz, 9H), 1.36 (d, J = 1.2 Hz, 3H), 2.27 (dd, J = 5.2, 12.6 Hz, 1H), 7.06 (tt, J = 1.2, 7.3 Hz, 1H), 7.13–7.20 (m, 3H), 7.28 (br t, J = 7.7 Hz, 2H), 7.34 (br d, J = 7.2 Hz, 2H), 7.43 (br d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ = 24.9 (d, J = 4.1 Hz), 26.6 (d, J = 33.7 Hz), 28.4 (d, J = 8.4 Hz), 31.5 (d, J = 13.9 Hz), 32.3 (d, J = 13.6 Hz), 33.5 (d, J = 26.5 Hz), 34.8 (d, J = 27.9 Hz), 40.6 (d, J = 13.1 Hz), 125.5, 126.1, 127.1, 128.1, 130.3 (d, J = 4.2 Hz), 131.2 (d, J = 1.6 Hz), 142.6 (d, J = 6.9 Hz), 144.0; ^{31}P NMR (202 MHz, CDCl_3): δ = 39.25; HR-MS (ESI): m/z = 353.2403, calcd. for $\text{C}_{24}\text{H}_{33}\text{P}$ $[\text{M} + \text{H}]^+$: 353.2398.

Typical Procedure for the Coupling Reaction of Aryl Halides with Amines

Aryl halide (1.1 equiv.) and amine (1 equiv.) were added to a solution of NaO-*t*-Bu (1.2 equiv.), $[(\pi\text{-allyl})\text{PdCl}]_2$ (0.5 mol%) and ligand 6 (2.0 mol%) in toluene (0.5 M) at room temperature under a nitrogen atmosphere. The mixture was stirred at 100–120 °C for the time specified. After cooling to room temperature, the reaction solution was diluted with toluene, washed with water, dried over anhydrous MgSO_4 and concentrated under reduced pressure. Purification of the concentrate by column chromatography on silica gel and/or recrystallization gave the coupling product.

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